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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/670,119	06/25/96	NE	[illegible]

HM32/0706

PATENT ADMINISTRATOR
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EXAMINER	
[illegible]	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/06/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/670119	Applicant(s) Ng et al
	Examiner Vaughes	Group Art Unit 1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 3/27/98.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 18, 20 - 37, 60-65 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 18, 20 - 37, 60-65 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 10

☐ Interview Summary, PTO-413

☐ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

DETAILED ACTION

Response to Amendment

1. The amendment filed 03/27/98 has been entered.

2. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1645.

3. The rejection of claims 19-20 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn due to cancelling claim 19 and amending claim 20.

4. The rejection of claim 22 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn due to the amendment of the claim.

5. Applicant's arguments filed 03/27/98 have been fully considered but they are not deemed to be persuasive.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 18, 20-36, and new/amended claims 37 & 60-65 are again rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons made of record, and as follows.

Applicants argue on pages 4-6 of the response that "the specification describes how to obtain an antagonist...", and "refers to many diseases which are known to be associated with overactivity of a particular receptor and in which, therefore, treatment with an antagonist of the function of that receptor would be desirable", and then lists six points to support their contention. In contrast to Applications assertions,

1) peptides "associated with specific receptor overactivity" have not been claimed; nor have they been adequately described. In contrast, the claims encompass any G-protein receptor dysfunction that also includes disease states in which "lack of activity", versus "overactivity", characterizes the disease state. For example, page 12, lines 19-22, mentions nothing about schizophrenia. Second, "abnormal functioning of D2 receptors" on page 20 is not equivalent to "overactivity", because a disease state such as Parkinson's disease is characterized by dopamine receptor inactivity, versus overactivity. Thirdly, the claims do not recite using any *specific* peptide to *specifically* "inhibit D2 receptors" in "schizophrenia, Huntington's Disease and/or Tourette's Syndrome", or during the noncharacterized "substance abuse" claimed. In other words, no measurable treatment of structurally defined "disorders" is claimed using *specific*

peptides, versus using structurally undefined fragments or analogues thereof. Thus, the skilled artisan would not know what, where, how and when Applicants' invention may be successfully practiced.

2) although adrenergic receptor antagonists may be accepted as therapeutic agents for treatment of hypertension (i.e., as described on page 23, lines 29-30), the specification provides apparently contradictory guidance on how "heart rate [can be decreased] using a β1-adrenergic-specific peptide" (pg. 41), because vehicle alone gave a comparable change in blood pressure when compared to administrating the β1-adrenergic-specific peptide (pg. 42). Thus, treatment of hypertension does not appear to work using these transmembrane peptide molecules (i.e., as it relates to claims 30-31). Accordingly, no functional assays are disclosed for practicing the full scope of that claimed (i.e., as it relates to using other types of adrenergic receptor, such a α1A; e.g., as it relates to claims 33-34), or for determining when treatment is effective or when needed; especially for any "disorder... characterized by disordered function of an integral membrane protein...". It is further noted that claims 30-31 specifically recite affecting β1-adrenergic receptors, in contrast to Applicants' assertions on page 6 of the response. The issue remains that the specification is clearly deficient in providing sufficient guidance for knowing how to effect measurable phenotype as it relates to any type of adrenergic receptor, without requiring undue experimentation to determine such, as previously made of record.

3) although theophylines may work on adenosine receptors as anti-asthmatics, and caffeine may have antidepressant effects though antagonizing adenosine receptors, the claims do not recite

using any *specific* peptide to *specifically* "decrease asthma" or "decrease depression" or "decrease arrhythmia" through "antagonizing *specific* adenosine receptors" (i.e., A1, A2a, A2b or A3), which are further unknown, or not adequately conceptualized within the instant specification, as it relates to specific disease states. As previously made of record, the specification provides no guidance on how to determine when a patient is in need of such treatment, nor what symptoms are envisioned to be treated, nor how the severity of these symptoms is related to the efficacy of an integral membrane receptor expression, nor how one would know when such administration is appropriate (e.g., as it relates to the disorders of claim 28 that have no known origin or cause); and especially when these disorders of the nervous system include neuronal cell damage that often results in cell death. Therefore, "administration" of any "peptide" molecule to treat neurons within the CNS requires solutions to selectively target responsive cells within the area of injury, and across the blood brain barrier, with a sufficient dosage of the specific peptide prior to neuronal cell death. However, neurons do not regenerate in the CNS (i.e., neurons die and thus can not be effectively treated; see Jackowski, pg. 305, last *pp*). Accordingly, there is no nexus for any expectation that merely administrating transmembrane-specific peptides for affecting one symptom of one disorder can be extrapolated to "treating" the full scope of symptoms encompassed by the current claims.

4) EGF receptors are not representative of all "neoplastic growth in cancer" because all neoplasms are not caused by dysfunction of the EGF receptor, or due necessarily to dysfunction of any different receptor; each with their own unique structure and mode of action. Nor are all

neoplasms derived from only "epithelial of fibroblastic cells", as Applicants appear to allude on page 5 of the response. Overall, the claims do not recite using any *specific* peptide to *specifically* "inhibit growth" of any tumor, whose etiology is otherwise unknown, and not disclosed. Thus, one skilled inthe art could not reasonably practice the invention as currently claimed, without undue experimentation to discover what defects cause cancer that may then be amenable to treatment using transmembrane peptides.

5) GABA receptors are not representative of any different population of neurons within the brain. Nor would these intrinsically inhibitory neurons be affected by antagonists to inhibit "overactivity", based solely on drugs such as benzodiazepines, because benzodiazepines bind to "agonist sites" (see pg. 27 of the specification), versus "antagonist sites", and increase chloride influx into GABA-nergic cells; thereby inhibiting action potentials, in contrast to Applicants' assertions. Thus, the specification provides contradictory evidence on how to determine how and when to successfully practice the invention, without requiring undue experimentation to discover how to make and use Applicants' invention. Accordingly, the claims do not recite using any *specific* peptide to *specifically* "inhibit GABA receptors" that effects any measurable phenotype, and as such merely represent an invitation to experiment.

6) The claims finally fail to recite using any *specific* peptide to *specifically* "inhibit dopamine and/or monoamine transporters" that effect any measurable cell type, disease state, or measurable phenotype; and as such merely constitutes an invitation to discover how to make and use Applicants' invention, thereby, not being enabled.

Applicants lastly argue on page 6 of the response that the phrase "effective fragment or analogue thereof" no longer appears in the amended claims. In contrast to Applicants' assertions, claims 18, 22g, 25h, 26h, 30h, 33h & 36 still recite or encompass such.

In summary, it is unknown and not disclosed what the metes and bounds "treating a disorder in a mammal" entails; nor how one would know when, or if, they have successfully practiced the invention "in a mammal", as broadly claimed, using any peptide, or any biologically functionally equivalent fragment or analogue of such, that "comprises at least one transmembrane domain", or "at least four consecutive amino acids from... any one of said plurality of transmembrane domains" (e.g., as it relates especially to claims 18 & 36). Clearly, the claims are not commensurate in scope with the limited guidance provided by the specification on how to successfully practice the instant invention without undue experimentation to discover how to make and use Applicants' invention; especially in this very unpredictable art of treating disease states that have their own unique, and unknown, etiologies.

8. Claims 62 & 64-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because tyrosine kinase receptors are metabotropic receptors, not channel proteins (i.e., as it relates to claim 62), nor transporter proteins (i.e., as it relates to claims 64-65); thereby, not further limiting the base claims.

9. Claims 18, 20-22, 36, and new claims 60-61, are again rejected under 35 U.S.C. 102(b) as being anticipated by Lofts et al., for the reasons made of record, and as follows.

Lofts et al. teach treatment of nude mice with an effective amount of a WT peptide sequence (see pg. 2814, Fig. 1), which comprises at least one transmembrane domain of the mammalian *neu*/EGF integral plasma membrane protein (i.e., as it relates to a plurality of transmembrane domains in a tyrosine kinase receptor which extends intracellularly; as recited in claims 18, 20-22, 36 & 60-61), such that growth of solid tumors in these mice was reduced (pgs. 2816-2817).

Applicants argue on page 7 of the response that the DNA sequences of Loft also encode "portions of the extracellular and intracellular sequences of this kinase". The Examiner agrees. However, in that the recitations "having at *least one* transmembrane domain" (e.g., claim 18) or the amended "at least four consecutive amino acids from... any *one of said plurality* of transmembrane domains" (e.g., as it relates to claims 18 & 36) clearly constitutes open claim language, Loft anticipates these claims, as previously made of record. It is noted that none of these claims recite "peptides limited to the amino acid sequence of the transmembrane domain".

10. Claims 18, 20-24, 29, 36, and new/amended claims 37 & 60-61, are again rejected under 35 U.S.C. 102(e) as being anticipated by Murphy et al., for the reasons made of record, and as follows.

Murphy et al. teach use of dopaminergic (col. 13, lines 29-49; i.e., as it relates to claims 22-24) and adrenergic (col. 16 line 60-col. 27, line 10; i.e., as it relates to claims 22-23 & 29) G-protein-coupled transmembrane receptor peptides in pharmaceutical compositions to "treat or prevent" G-protein-related diseases (cols. 35-37; as it relates to claims 18-21, 36-37 & 60-61).

Applicants argue on pages 8-9 of the response that the mechanism of action of Murphy's peptides is not the same as the instant invention. However, this is immaterial to the rejection made of record, because Murphy's peptides structurally meet the claim limitations of "have at least one transmembrane domain" (e.g., claim 18), or "at least four consecutive amino acids from... any one of said plurality of transmembrane domains" (e.g., as it relates to claims 18 & 36). Thus, Murphy clearly anticipates these claims for the reasons made of record.

Applicants then argue on page 9 of the response that "[n]ot all receptor activity, however, requires binding of a ligand to a receptor", and then argues that "a number of disease states have been described in which membrane receptors have been found to be constitutively active, leading to a disease state". The Examiner agrees. However, no limitations are recited that distinguishes the teachings of Murphy from the instant invention, as broadly claimed. Thus, the claims encompass the teachings of Murphy et al., for the reasons made of record.

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11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and on alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RCH

Robert C. Hayes, Ph.D.
June 18, 1998

PATRICIA DUFFY
PATENT EXAMINER
PRIMARY